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The effectiveness of propranolol in treating infantile haemangiomas: a meta-analysis including 35 studies

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Propranolol has shown excellent results in treating infantile hemangiomas of all sites of the body, but this conclusion remains controversial.

WHAT THIS STUDY ADDS

- This meta-analysis has provided strong evidence that propranolol is better than other treatment modalities for the resolution of infantile hemangiomas of all sites of the body for the first time.

AIMS

Propranolol may have shown excellent results as a first line therapy in infantile haemangiomas (IHs) at all sites in the body, but this conclusion remains controversial. In an attempt to resolve this issue, we performed a meta-analysis.

METHODS

A search of the literature using PubMed, MEDLINE, Cochrane Library databases and China National Knowledge Infrastructure (CNKI) was performed to identify studies which estimated the efficacy of propranolol therapy in infants with haemangiomas all sites of the body. The pooled odds ratio (OR) along with the corresponding 95% confidence intervals (CI) were assessed using a fixed effects model.

RESULTS

Thirty-five studies involving 324 infantile haemangioma(IH) patients and 248 controls were retrieved and analyzed. The efficacy of propranolol was greater than other therapies in treating IHs (OR = 9.67, 95% CI 6.62, 14.12, $P < 0.001$). In a stratified analysis by sites of tumour, propranolol was a more effective therapy when compared with steroids (OR = 9.67, 95% CI 6.61, 14.15, $P < 0.001$), vincristine (OR = 9.00, 95% CI 2.15, 37.66, $P = 0.003$) and laser treatment (OR = 9.00, 95% CI 1.42, 57.12, $P = 0.020$) in treating cutaneous IHs (OR = 24.95, 95% CI 9.48, 65.64, $P < 0.001$), peri-ocular IHs (OR = 9.39, 95% CI 3.88, 22.71, $P < 0.001$), infantile airway haemangiomas (OR = 20.91, 95% CI 7.81, 55.96, $P < 0.001$) and infantile hepatic haemangiomas (OR = 9.89, 95% CI 1.20, 81.54, $P = 0.033$).

CONCLUSION

The current meta-analysis provided strong evidence for propranolol as a first line therapy for IHs.

Introduction

Infantile haemangiomas (IHs) are the most common benign tumour of infancy, occurring in approximately 4% to 10% of infants [1]. Typically, IHs usually grow rapidly during the first 3 to 12 months of age, and may take 3 to 7 years to spontaneous involute [2]. Frequently IHs are superficial, involving only skin and subcutaneous tissue, although a minority can be problematic and even life threatening. Ulceration, scarring, recurrent bleeding and functional impairment may complicate untreated IHs [3]. Therefore, most IH cases require no treatment, but if functional impairment and/or ulceration arise or there are dramatic aesthetic issues, treatment is needed [4].

Therapeutic options for IHs have centred upon systemic and intralesional steroids, interferon, vincristine, bleomycin, lasers and/or surgical excision treatment being reserved for troublesome and severe haemangiomas [5, 6]. Until now, systemic steroids are considered as first line therapy for such problematic and function threatening haemangiomas, but long term steroid usage may bring many side effects, including growth disturbances, irritability, hypertension, immune system dysfunction and Cushingoid changes. Moreover, the response rate to steroids is variable. Other treatment modalities are second line considerations and are relatively less used because of inconsistent efficacy, adverse effects and toxicity [4, 7].

In 2008, propranolol, a non-selective β-adrenoceptor blocker, was serendipitously discovered for the treatment of cutaneous IHs when used to treat cardiopulmonary conditions by Léauté-Labrèze *et al*. [8]. Oral propranolol therapy for haemangiomas has dramatically changed the strategies of treatment used to date. Since then, several institutions worldwide have initiated propranolol therapy for IHs and gained experience with this therapy. During the following years, investigators have found propranolol to be an effective treatment for IHs at all sites in the body [9–11]. Multiple reports have confirmed that propranolol is more efficient in managing IHs, has a more rapid response rate and fewer side effects.

Several investigators have published studies supporting propranolol as the first line therapy for IHs [12]. However, these results are still controversial. Menezes *et al*. kept a sceptical attitude to propranolol in treating IHs [13]. Furthermore, there are several reports supporting steroids which have been used to treat IHs for over 40 years and have been shown to be more suitable in treating IHs [14].

In 2011, Peridis *et al*. [15] performed a meta-analysis and demonstrated that propranolol therapy was more effective than other treatment modalities in treating infantile airway haemangiomas. However, there were some limitations in their work. For instance, the paper only estimated the effectiveness of treatments on infantile airway haemangiomas, and not other sites of haemangiomas. In addition, the literature was not retrieved completely. Several cases which did not report the effectiveness of treatments or patients who were started on propranolol and other therapies at the same time were still included in their study which inevitably influenced the results.

The current meta-analysis encompassing 35 studies with 324 IH patients and 248 controls aims to derive a more precise estimate of the effectiveness of propranolol compared with other therapies. We also performed a subgroup analyses by sites of haemangiomas, not just in infantile airway haemangiomas. Therefore, our work could provide a more comprehensive understanding for clinicians.

Methods

Search strategy

A systematic search of the literature using PubMed, MEDLINE, Cochrane Library databases and China National Knowledge Infrastructure (CNKI) was performed to identify studies using combinations of the following search terms: 'haemangioma', 'propranolol', 'infantile', 'children', 'steroids', 'corticosteroids', 'vincristine', 'laser', 'interferon', 'cyclophosphamide', 'bleomycin' and 'treatment'. All of the studies were published from their earliest entry points to October 2012.

Selection

Searches were restricted to studies published in English, French and Chinese. The studies had to meet the following major criteria: (i) IHs, (ii) propranolol and other modalities were used in the treatment of haemangiomas and (iii) the efficacy of propranolol and other treatments was assessed in the treatment of IHs. The cases which were initially treated with a combination of propranolol and other treatments were excluded. The efficacy of propranolol and other treatments which was not clearly reported were excluded. When the same results were reported in several papers, only the most recent publication study was included in the meta-analysis. Unpublished reports and abstracts were not considered.

Data extraction

The extracted data included first author's name, year of publication, total number of case patients and total number of control subjects, characteristics of the sample population, treatment modalities, outcome of treatments, length of time and length of follow-up. Data from each study were extracted and recorded on multiple worksheets.

Statistical analysis

Odds ratio (OR) with 95% confidence interval (CI) was used to combine the data. The statistical significance of the summary OR was determined with the Z-test. Heterogene-

ity among studies was assessed using the chi-square based Q statistic ($P < 0.1$ for the Q test indicates significant heterogeneity) [16]. We also quantified the effect of heterogeneity using the I^2 statistic [17], I^2 values of 25, 50, and 75% were defined as low, moderate and high estimates, respectively. Either a random effects model (DerSimonian-Laird method [18]) or fixed effects model (Mantel-Haenszel method [19]) was used to calculate pooled effect estimates in the presence or absence of heterogeneity, respectively.

Finally, potential publication bias was evaluated through funnel plot visual analysis and with the Begg's and Egger's tests [20, 21]. $P < 0.05$ was considered statistically significant. For possible publication bias, we used the trim and fill method to evaluate the influence on the results. All statistical analyses were performed by STATA version 10 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of the included studies

The computerized search using the above search strategy delivered 373 publications describing outcome of treatments in treating IHs. 79 studies describing IHs treated with propranolol and other treatments were identified. Of these, 37 papers were excluded due to unclear reports of the effectiveness of propranolol and other treatment modalities. Subsequently, seven studies were excluded because of initial treatment with a combination of propranolol and other treatment modalities (Figure 1). Data from the 35 reports consisting of 324 IH patients and 248 controls matching the inclusion and exclusion criteria were included in current meta-analysis [4, 8–11, 22–51]. Of these, 34 studies with 323 IH patients and 247 controls compared the efficacy of propranolol and steroids in treating IHs, 10 studies with 10 IH patients and 10 controls compared the propranolol *vs.* a vincristine subgroup and six studies with six IH patients and six controls compared propranolol *vs.* a laser subgroup. 15 studies with 52 IH patients and 52 controls compared the efficacy of propranolol and other treatment modalities in the cutaneous IH subgroup, seven studies with 66 IH patients and 35 controls in the peri-ocular IH subgroup, 16 studies with 45 IH patients and 45 controls in the infantile airway haemangioma subgroup and four studies with six IH patients and six controls in the infantile hepatic haemangioma subgroup. The characteristics of the included studies are shown in Table 1.

Pooled analyses

Propranolol vs. *other treatments for treating IHs* 35 papers with a total number of 324 IH cases and 248 controls compared the effectiveness of propranolol with other treatments in treating IHs. Heterogeneity among the studies was absent (Q = 43.12, I^2 = 23.5%, P = 0.112). The Forest plot (Figure 2) revealed that propranolol was a more effective therapy in treating IHs than other treatments (OR = 9.67, 95% CI 6.62, 14.12, $P < 0.001$).

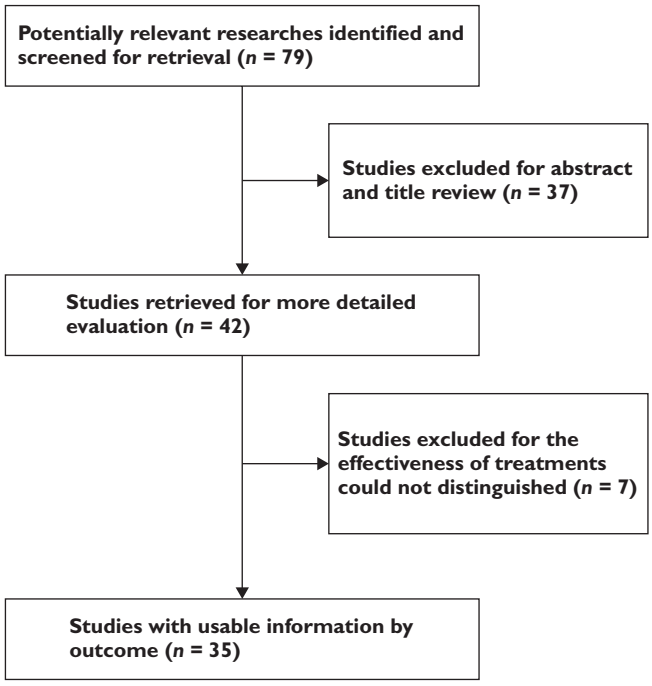

Figure 1
Flow diagram of the selection process for the articles

Propranolol vs. *steroids for treating IHs* A total of 34 papers including 323 IH cases and 247 controls were available for the evaluation of the efficacy of propranolol and steroids. There was no heterogeneity among the studies (Q = 43.12, I^2 = 25.8%, P = 0.091). The combined results demonstrated that propranolol therapy was more effective than steroids in treating His (OR = 9.67, 95% CI 6.61, 14.15, $P < 0.001$) (Figure 3).

Propranolol vs. *vincristine for treating IHs* 10 papers including 10 IH cases and 10 controls for the comparison of the efficacy of propranolol and vincristine in treating IHs were found. Between study heterogeneity was absent (Q = 0.00, I^2 = 0.0%, P = 1.00). The combined OR was 9.00 (95% CI 2.15, 37.66, P = 0.003) (Figure 4), demonstrating that propranolol was more effective than vincristine.

Propranolol vs. *laser for treating IHs* There were six papers including six IH cases and six controls comparing the efficacy of propranolol and laser for treatment of IHs. Heterogeneity among the studies was not remarkable (Q = 0.00, I^2 = 0.0%, P = 1.00) and propranolol therapy was more effective when compared with laser (OR = 9.00, 95% CI 1.42, 57.12, P = 0.020) (Figure 5).

The effectiveness of propranolol compared with other treatments might be affected by the site of the tumour.

Table 1

The characteristics of the 35 eligible studies

Study (year)	Number of patients (M/F)	Mean age (months)	Sites	Therapy 1 Treatment (number of patients)	Mean duration (months)	Result (number of patients)	Therapy 2 Treatment (number of patients)	Mean duration (months)	Result (number of patients)
Harikrishna *et al.* (2011) [22]	2 (0/2)	15.5	Skin, eye	Steroids (2)	NR	Low improvement	Propranolol (2)	11	Evident improvement
Manunzam *et al.* (2010) [23]	9	5.8	NR	Steroids (9)	NR	Low improvement	Propranolol (9)	12	Evident improvement
Solomon *et al.* (2011) [24]	1	NR	Skin	Steroids (1), vincristine (1)	NR	No effect	Propranolol (1)	NR	Improvement
Corapcioğlu *et al.* (2011) [25]	12 (3/9)	4.5	NR	Steroids (12)	4	Low improvement	Propranolol (12)	5	Evident improvement
Ghosh & Ghosh (2012) [26]	1 (0/1)	1.5	Skin, liver	Steroids (1)	NR	Low improvement	Propranolol (1)	NR	Evident improvement
Fuchsmann *et al.* (2011) [27]	17	12.6	Skin, airway	Steroids (17), laser (1)	NR	Stabilization (2). rebound growth (1), no effect (14)	Propranolol (17)	7.2	Improvement (16), rebound growth (1)
Sarialioglu *et al.* (2010) [28]	1 (1/0)	7	Liver	Steroids (1), vincristine (1), interferon-α (1)	3	low improvement	propranolol (1)	>3	Evident improvement
Breur *et al.* (2011) [29]	1 (0/1)	1	Skin	Steroids (1)	>18	Rebound growth	Propranolol (1)	NR	Improvement
Rosbe *et al.* (2010) [30]	2	1.5	Skin, airway	Steroids (2), laser (1), vincristine (1)	NR	Low improvement (1), rebound growth (1)	Propranolol (2)	NR	Evident improvement
Mazereeuw-Hautier *et al.* (2010) [11]	3	NR	Liver	Steroids (3), vincristine (1)	NR	No effect (2), mprovement (1)	Propranolol (3)	NR	Evident improvement
Mistry & Tzifa (2010) [31]	1 (0/1)	1.2	Airway	Steroids (1)	NR	Low improvement	Propranolol (1)	>3.2	Evident improvement
Truong *et al.* (2010) [32]	1 (0/1)	1.2	Airway	Steroids (1), laser (1)	3	Rebound growth	Propranolol (1)	5	Improvement
Maturo *et al.* (2010) [33]	1 (0/1)	3	Airway	Laser (1)	NR	Low improvement	Propranolol (1)	>6	Evident improvement
Léauté-Labrèze *et al.* (2008) [8]	4 (2/2)	Newborn	Skin	Steroids (4)	5.1	Stabilization (2), no effect (1), rebound growth (1)	Propranolol (4)	8.7	Evident improvement
Durr *et al.* (2012) [9]	2 (0/2)	NR	Airway	Steroids (2), laser (1), vincristine (1)	NR	Low improvement (1), improvement (1)	Propranolol (2)	12	Evident improvement
Raol *et al.* (2011) [34]	2 (0/2)	1	Skin, airway	Steroids (2)	>12	No effect	Propranolol (2)	14.5	Improvement (1), no effect (1)
Javia *et al.* (2011) [35]	10 (2/8)	3	Airway	Steroids (10)	NR	Low improvement	Propranolol (10)	9	Low improvement (3), improvement (7)
Moss *et al.* (2012) [10]	1 (1/0)	NR	Eye	Steroids (1)	>4	Low improvement	Propranolol (1)	11	Evident improvement
Yeh *et al* (2011) [36]	2 (1/1)	1	Skin	Steroids (2), vincristine (1)	NR	Improvement (1), rebound growth (1)	Propranolol (2)	NR	Evident improvement
Taban & Goldberg (2010) [37]	1 (0/1)	1.5	Eye	Steroids (1)	1	Low improvement	Propranolol (1)	3	Improvement
Leboulanger *et al.* (2010) [51]	11	2.4	Airway	Steroids (11), vincristine (1)	NR	Low improvement	Propranolol (11)	6	Evident improvement
Cheng *et al.* (2010) [38]	2 (1/1)	2.2	Skin, eye	Steroids (2)	NR	Low improvement	Propranolol (2)	9	Evident improvement
Marsciani *et al.* (2010) [39]	1 (0/1)	2	Liver	Steroids (1), vincristine (1)	>3	Low improvement	Propranolol (1)	>1	Evident improvement
Denoyelle *et al.* (2009) [40]	2 (0/2)	1	Skin, airway	Steroids (1), vincristine (1)	NR	Low improvement	Propranolol (2)	NR	Evident improvement
Blanchet *et al.* (2010) [41]	1 (0/1)	3	Skin, airway	Steroids (1)	NR	Improvement	Propranolol (1)	NR	Evident improvement
Theletsane *et al.* (2009) [42]	1 (0/1)	0.5	Skin, airway	Steroids (1)	1.5	Low improvement	Propranolol (1)	>6	Evident improvement
Sans *et al.* (2009) [43]	13 (5/8)	2–41	Skin, eye, airway	Steroids (13)	NR	Low improvement	Propranolol (13)	NR	Evident improvement
Jephson *et al.* (2009) [44]	1 (0/1)	4	Airway	Steroids (1)	NR	Low improvement	Propranolol (1)	9	Evident improvement
Price *et al.* (2011) [45]	139 (32/107)	4.7	NR	Steroids (42)	5.2	Improvement (12), low improvement (30)	Propranolol (68)	7.9	Improvement (56), low improvement (12)
Bertrand *et al.* (2011) [46]	24	3.7	Skin, eye	Steroids (12)	12.7	Low improvement (12)	Propranolol (12)	10.6	Evident improvement (12)
Jin *et al.* (2011) [47]	73 (20/53)	10	NR	Steroids (31)	NR	Improvement (18) low improvement (13)	Propranolol (42)	NR	Improvement (34), low improvement (8)
Xiong *et al* (2012) [48]	52 (27/25)	1–26	E ye	Steroids (21)	NR	Improvement (9), low improvement (12)	Propranolol (31)	NR	Improvement (25), low improvement (6)
Ji *et al.* (2012) [49]	46 (17/29)	7	NR	steroids (19)	NR	Improvement (4), low improvement (15)	Propranolol (27)	NR	Improvement (6), low improvement (21)
Liang & Yu (2012) [50]	32 (13/19)	6.5	NR	Steroids (16)	6	Improvement (3), low improvement (13)	Propranolol (16)	6	Improvement (6), low improvement (10)
Buckmiller *et al.* (2009) [4]	1 (0/1)	2	Airway	Steroids (1), laser (1), vincristine (1)	20	Low improvement	Propranolol (1)	>4	Evident improvement

F, female; M, male; NR, not reported.

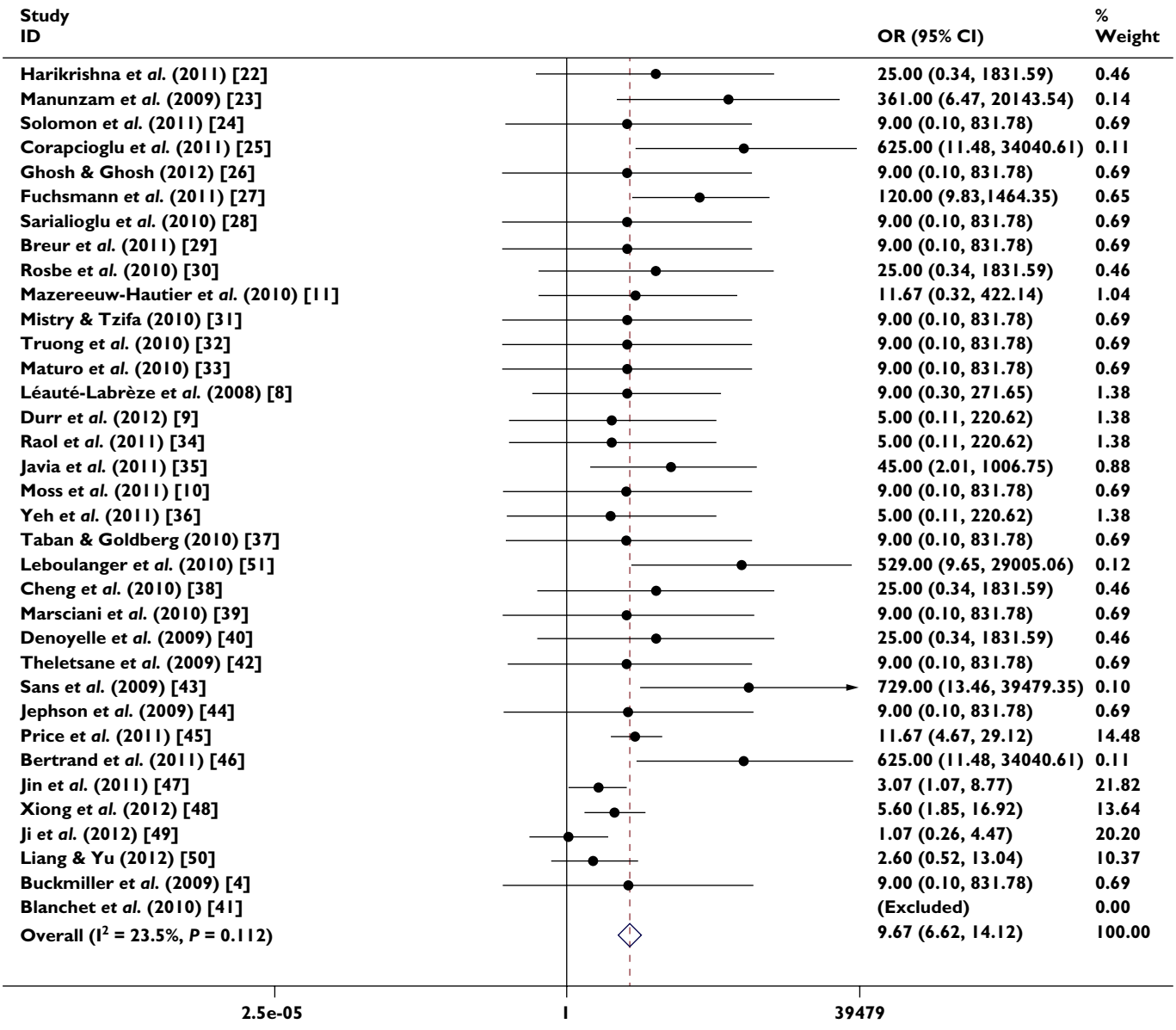

Figure 2

Forest plot of the effectiveness of propranolol compared with other treatments in treating IHs

Accordingly, subgroup analysis was stratified into cutaneous haemangiomas, peri-ocular haemangiomas, airway haemangiomas and hepatic haemangiomas.

Propranolol vs. *other treatments for treating cutaneous IHs* 15 articles compared the efficacy of propranolol and other treatment modalities in the cutaneous IH subgroup. Heterogeneity among studies was not significant (Q = 7.00, I^2 = 0.0%, P = 0.902). The results suggested that propranolol therapy was more effective than other treatments in the cutaneous IH subgroup (OR = 24.95, 95% CI 9.48, 65.64, P < 0.001) (Figure 6).

Propranolol vs. *other treatments for treating peri-ocular IHs* Seven articles including 66 IH cases and 35 controls evaluated the treatments in peri-ocular IHs. There was no significant heterogeneity among studies (Q = 3.58, I^2 = 0.0%, P = 0.734). The Forest plot (Figure 7) revealed that the effectiveness of propranolol was more significant in the peri-ocular IH subgroup (OR = 9.39, 95% CI 3.88, 22.71, P < 0.001).

Propranolol vs. *other treatments for treating infantile airway haemangiomas* 16 studies with 45 IH cases and 45 controls compared the efficacy of propranolol with

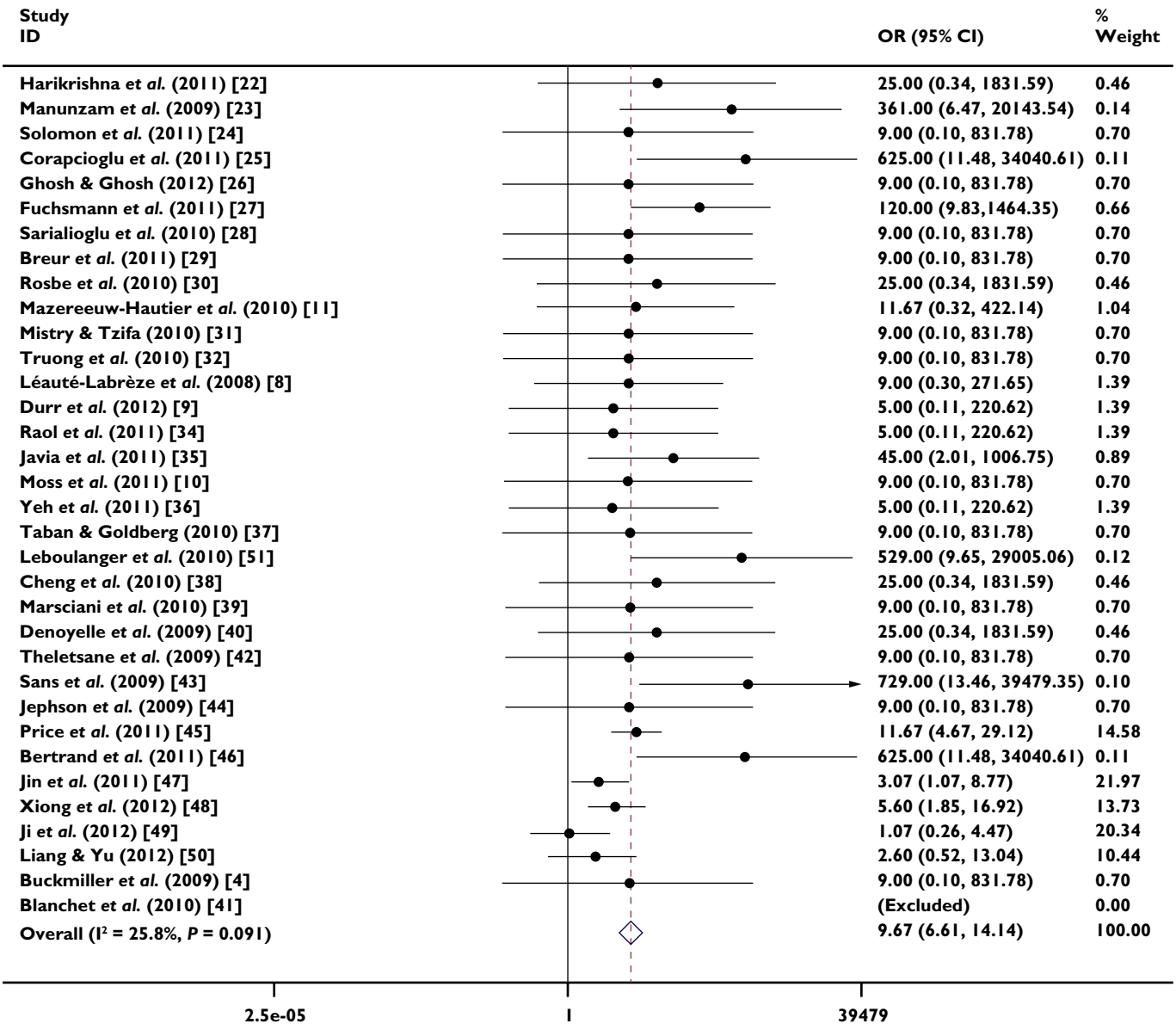

Figure 3

Forest plot of the effectiveness of propranolol compared with steroids in treating IHs

other treatment modalities in treating airway IHs. Heterogeneity was absent (Q = 5.00, I^2 = 0.0%, P = 0.986). Propranolol therapy was more effective in treating infantile airway haemangiomas (OR = 20.91, 95% CI 7.81, 55.96, $P <$ 0.001) (Figure 8).

Propranolol vs. *other treatments for treating infantile hepatic haemangiomas* Six IH cases and six controls from four studies evaluated the efficacy of treatments in hepatic IHs. Between study heterogeneity was not remarkable (Q = 0.01, I^2 = 0.0%, P = 1.00). For treating hepatic IHs, propranolol was a significantly more effective therapy than other treatments (OR = 9.89, 95% CI 1.20, 81.54, P = 0.033) (Figure 9).

Six randomized controlled trials (RCTs) which consisted of four Asian studies and two Caucasian studies were included in the current meta-analysis [45–50]. Subgroup analyses by RCT studies were performed. In these studies, degree of clinical improvement in appearance (including colour and size) was defined as follows: slight (<25%), moderate (25–50%), good (50–75%) or excellent (>75%). We conducted subgroup analyses by the good group and excellence group to compare the effectiveness between the propranolol therapy and steroid therapy in treating IHs.

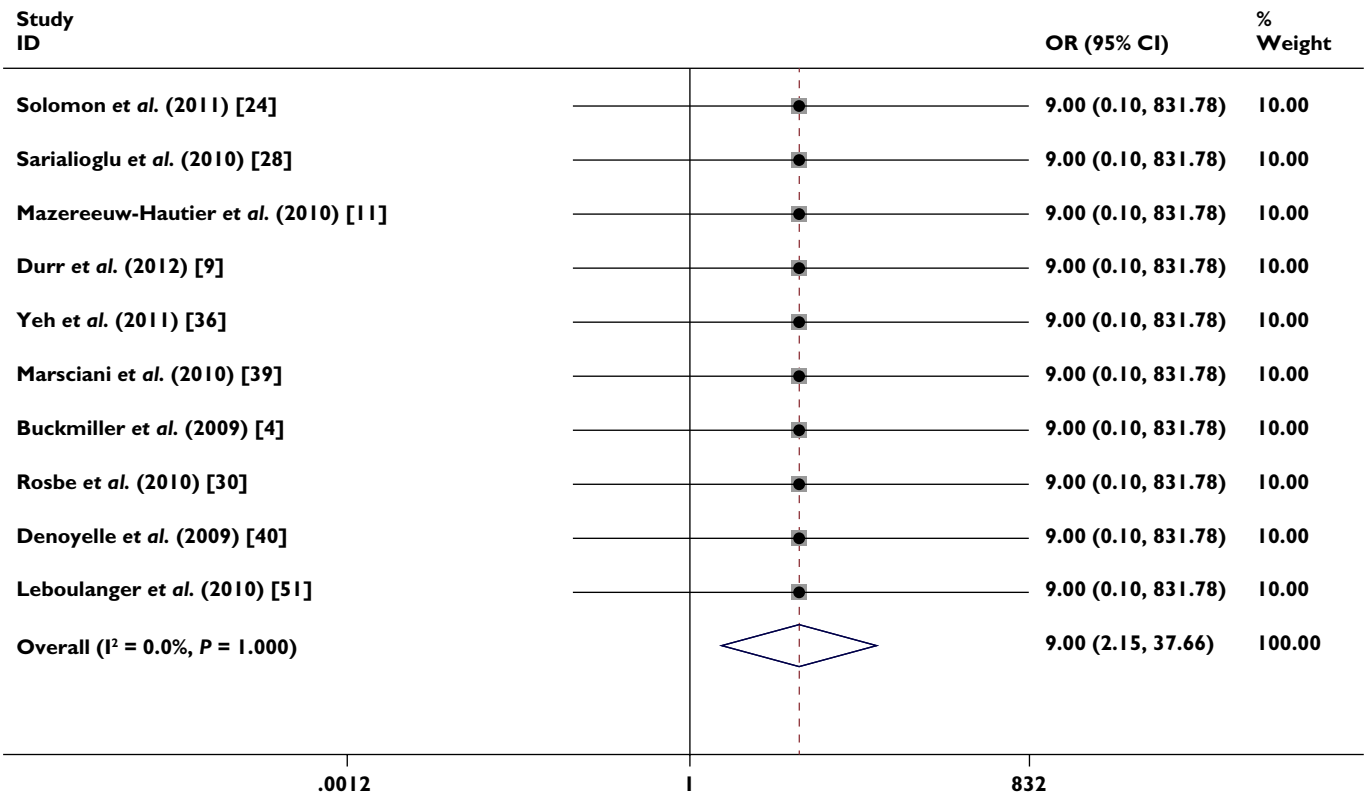

Figure 4

Forest plot of the effectiveness of propranolol compared with vincristine in treating IHs

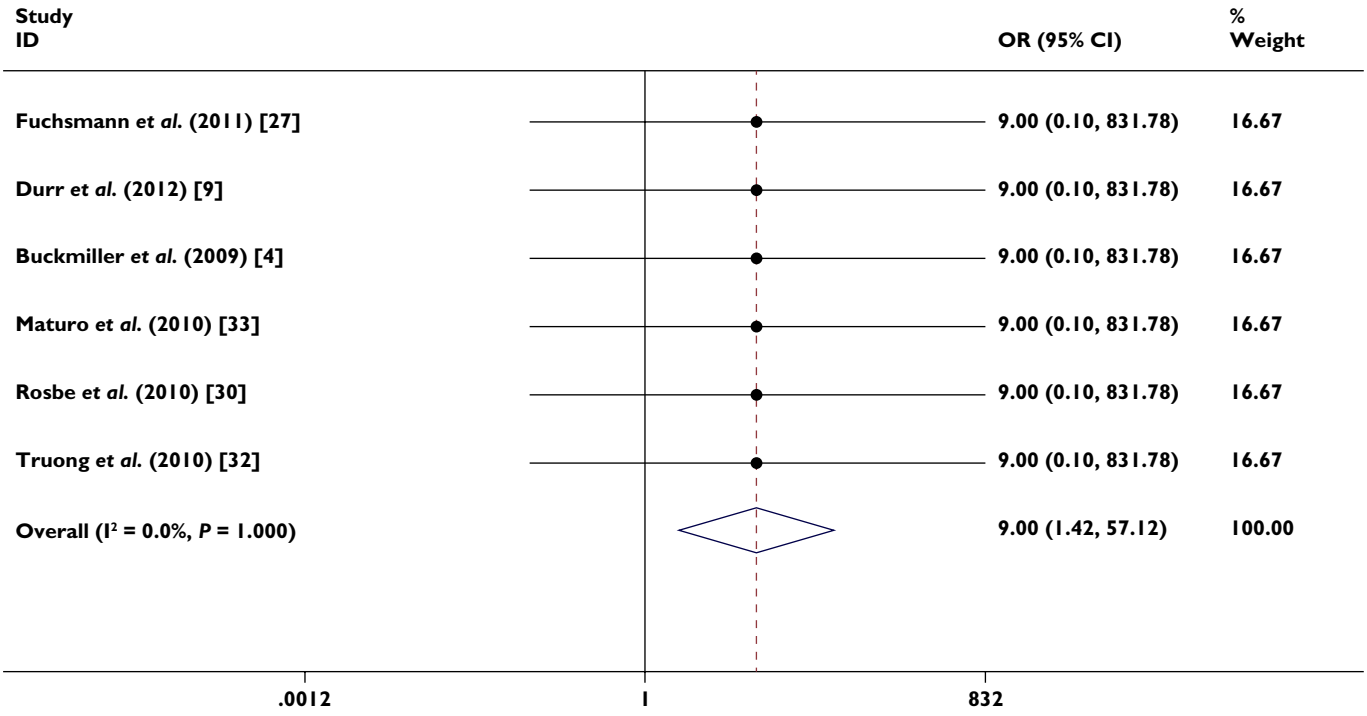

Figure 5

Forest plot of the effectiveness of propranolol compared with laser in treating IHs

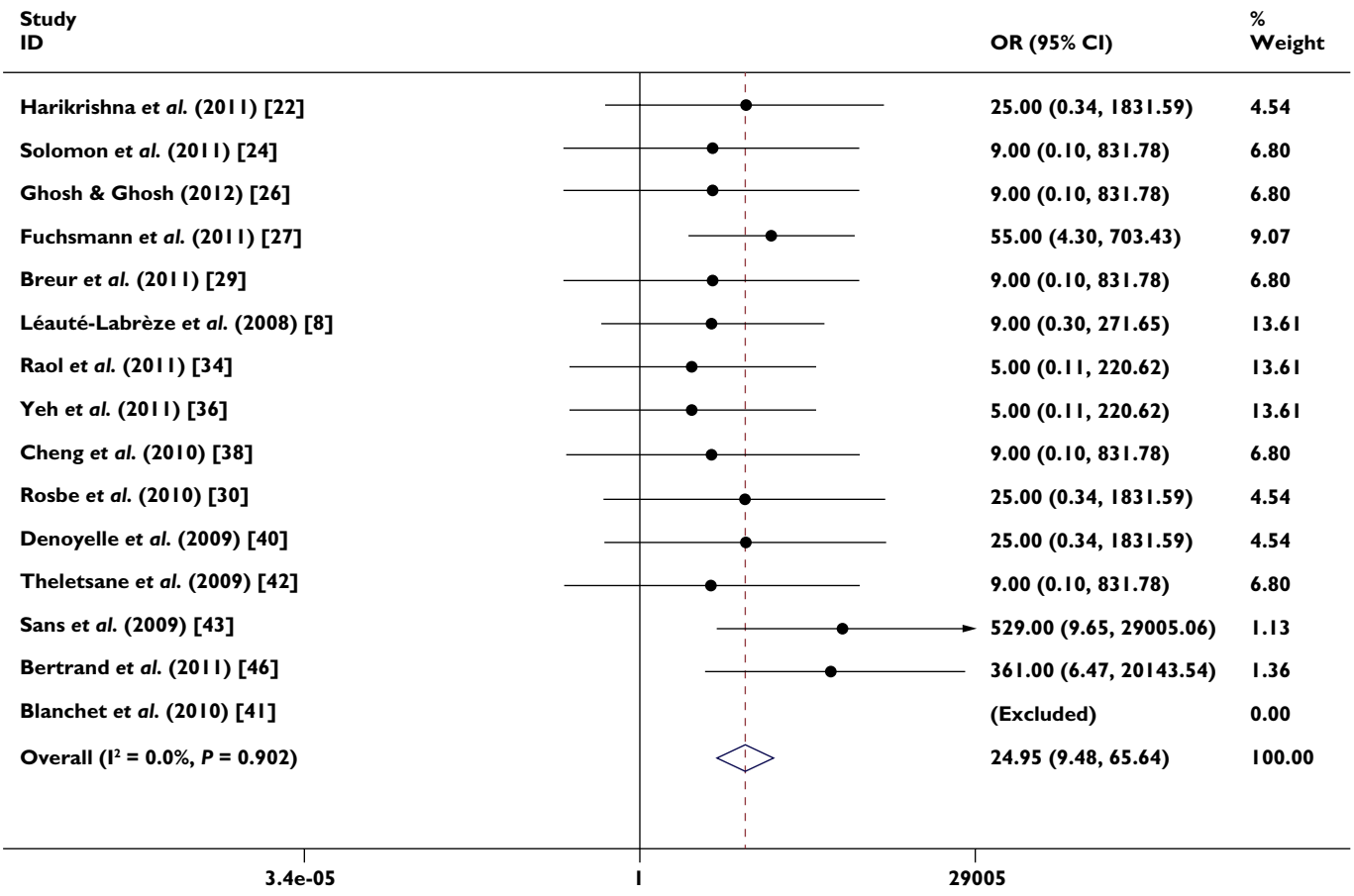

Figure 6
Forest plot of the effectiveness of propranolol compared with other treatments in treating cutaneous IHs

Propranolol vs. *steroids for treating IHs in the good group* Six studies including 196 IH cases and 141 controls were included in the subgroup analysis by good degree group. Heterogeneity among the studies was not remarkable (Q = 8.91, I^2 = 43.9%, *P* = 0.113). For treating IHs, propranolol therapy was more effective than steroid therapy (OR = 8.28, 95% CI 4.79, 14.30, *P* = 0.000; Figure 10).

Propranolol vs. *steroids for treating IHs in the excellence group* Five studies including 184 IH cases and 129 controls were included in the excellence group subgroup analysis. Significant between study heterogeneity was detected (Q = 9.83, I^2 = 59.3%, *P* = 0.043). The Forest plot (Figure 11) revealed that propranolol therapy was more effective in the subgroup analysis in the excellence group (OR = 3.66, 95% CI 1.54, 8.76, *P* = 0.003).

Stratified analysis by ethnicity was performed in order to determine the source of heterogeneity among the studies. Significant between study heterogeneity was not found in the Asian population (Q = 2.95, I^2 = 0.0%, *P* = 0.399). There was only one Caucasian study and therefore subgroup analysis was not performed in Caucasians.

Bias diagnostics

Both Begg's test and Egger's test were performed to assess the publication bias of the literature. We found a potential publication bias in the comparison of propranolol *vs.* other treatments (P_{Egger} = 0.006) and propranolol *vs.* steroids (P_{Egger} = 0.006). By using the trim and fill method, we showed that, if the publication bias was the only source of the funnel plot asymmetry, it needed 16 more studies to balance the funnel plot. The adjusted risk estimate was attenuated but remained significant (propranolol *vs.* other treatments: OR = 4.12, 95% CI 2.18, 7.79, *P* < 0.001; propranolol *vs.* steroids: OR = 4.05, 95% CI 2.12, 7.73, *P* < 0.001), indicating the stability of our results.

Discussion

In the current meta-analysis of 324 IH patients and 248 control subjects, the major finding was that the effectiveness of propranolol was probably better than other treatment modalities for the resolution of IHs. Furthermore, in the subgroup analysis by site of tumour, propranolol

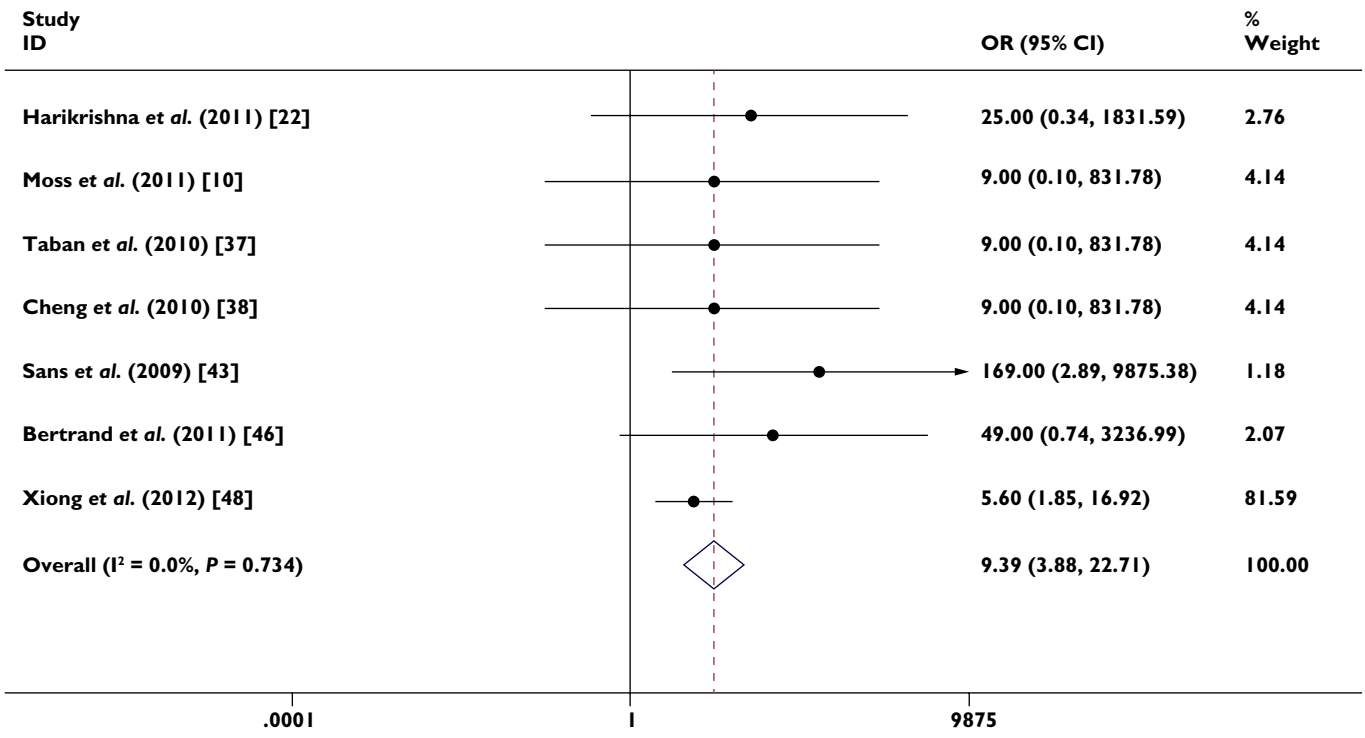

Figure 7

Forest plot of the effectiveness of propranolol compared with other treatments in treating peri-ocular IHs

therapy was also more effective when compared with other treatments. In clarifying a comparison between the effect of propranolol and other therapies in treating IHs, the quality of study design is great importance. Therefore, inappropriate materials may result in insufficient statistical power. RCT data are usually included for meta-analyses. Nevertheless, propranolol therapy was more effective than steroid therapy in treating IHs in subgroup analyses when the analyses were restricted to RCT studies.

Steroid treatment is considered as a long, established, first line therapy for IHs. It may be administered systemically or locally, and has been shown to be of limited benefit with only about a third of cases responding, a third of patients responding equivocally and the remaining third having continued growth [52–55]. Side effects of long term steroid usage are severe, including growth retardation, immunosuppresion, hypertension, risk of infection and Cushingoid changes [56, 57]. The reported response rates are variable for treating IHs using the second line treatments such as lasers, vincristine, interferon-α, bleomycin and cyclophosphamide, which are generally used when haemangiomas are resistant to steroid treatment [58]. Surgical excision of IHs is considered only for patients who present with life threatening complications, such as difficulty in breathing and hepatomegaly caused by large numbers of tumours in the airways or liver.

The superiority of propranolol therapy compared with other treatments is that it shows high efficacy, low severe complication rate and rapid clinical improvement, sometimes as early as 24 h, which may be evident in the majority of patients within the first week of treatment [23, 43, 58]. Propranolol has a well-documented safety and side effect profile. However, propranolol should be used with caution for the first several doses, especially in children, due to potential side effects including bradycardia, hypotension, hypoglycaemia, fatigue, bronchospasm, congestive heart failure and gastrointestinal discomfort/reflux. Hospitalization with monitoring for the first week should be the optimum selection. As regards dose, 2 mg kg^{-1} day^{-1} appears to work extremely well without side effects. However, the aforementioned adverse effects are seen at doses >2 mg kg^{-1} day^{-1} [4].

The molecular mechanism of action of propranolol in treating IHs is probably that of reduced expression of vascular endothelial growth factor and fibroblast growth factor in proliferation in the endothelial cell [43, 59]. Propranolol is also thought to cause vasoconstriction in the supplying capillaries through its inhibitory effect on the production of nitric oxide and to induce apoptosis because of its action on the caspase cascade [60].

The current meta-analysis results were generally consistent with the results by Peridis *et al*. in infantile airway haemangiomas [15]. However, there were several differences between the two studies. In a stratified analysis of infantile airway haemangiomas, two studies by Truong *et al*. [61] in which the results were not clearly reported

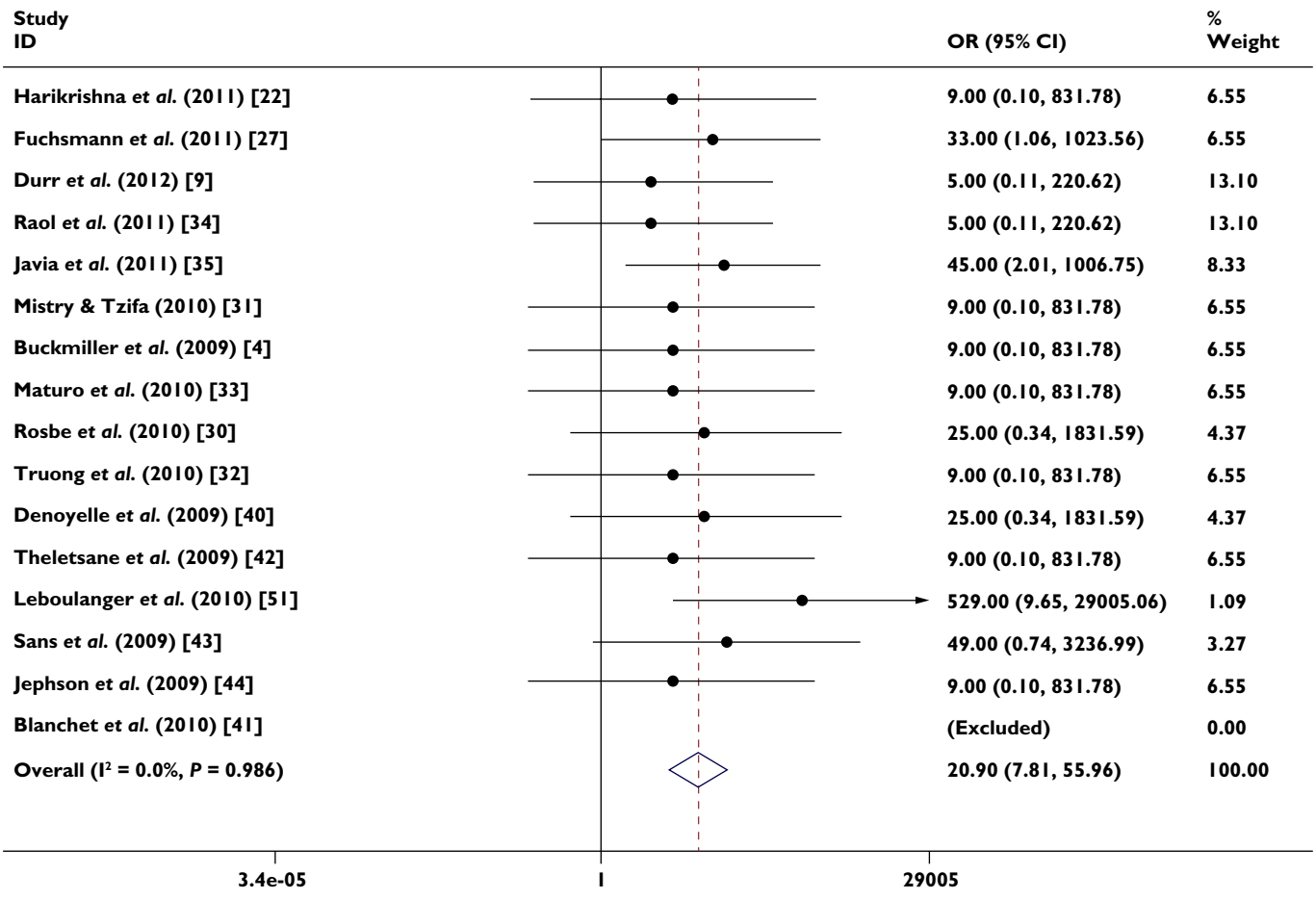

Figure 8

Forest plot of the effectiveness of propranolol compared with other treatments in treating infantile airway haemangiomas

and Manunza *et al*. [23] in which several groups were started on propranolol and other therapies at the same time and therefore deviated from the inclusion criteria were not excluded from Peridis *et al*.'s research but were excluded from the current study. An additional five studies were included in our article. Moreover, the present study performed several stratified analyses to prove that propranolol was more effective than other treatment modalities in IH therapy at all sites in the body. In addition, we conducted subgroup analyses of RCT studies to clarify the comparison between the effect of propranolol and steroid therapy effect in treating IHs. Therefore, our meta-analysis has a stronger evidence to clarify the associations.

Publication bias is a well-known problem. We found a potential publication bias in the comparison of propranolol *vs.* other treatments and propranolol *vs.* steroids. The may arise for many reasons. For instance, our meta-analysis took into consideration only fully published studies. Positive results tend to be accepted by journals. Besides, language bias may have existed. We should point out that the publication bias may partly account for the result, but the conclusion may not be greatly affected by the publication bias. When we accounted for publication bias using the trim and fill method, the adjusted risk estimate was attenuated but remained significant, indicating the stability of our results. Therefore the summary statistics obtained may approximate the actual average.

Between study heterogeneity is a well known problem that is unavoidable. In our meta-analysis, heterogeneity was detected in the subgroup analysis in the RCT studies excellence group. The source of heterogeneity may arise from many aspects, such as the region of study, the sample size and other factors. In order to explain the main reasons for the heterogeneity across studies, stratified analysis by ethnicity was performed. The result showed that no significant heterogeneity was observed in the Asian population subgroup, suggesting heterogeneity could be partly explained by ethnicity.

However, there are some limitations in our study. Firstly, the majority of papers included were case reports

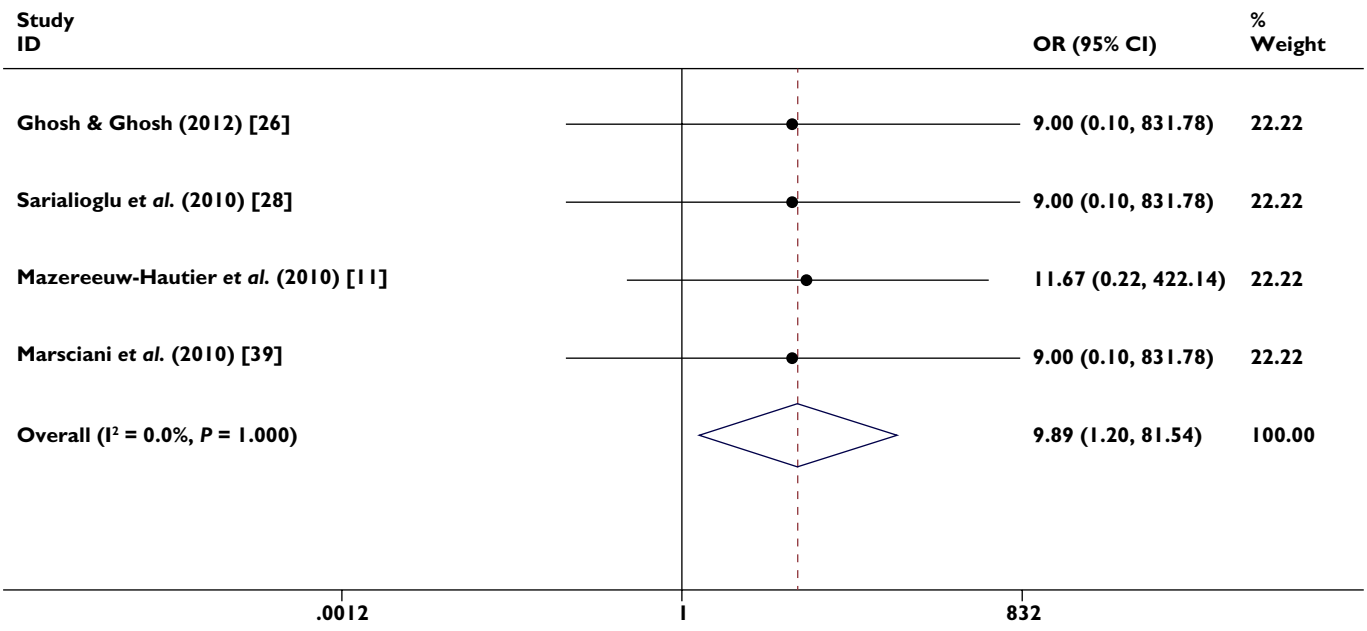

Figure 9

Forest plot of the effectiveness of propranolol compared with other treatments in treating infantile hepatic haemangiomas

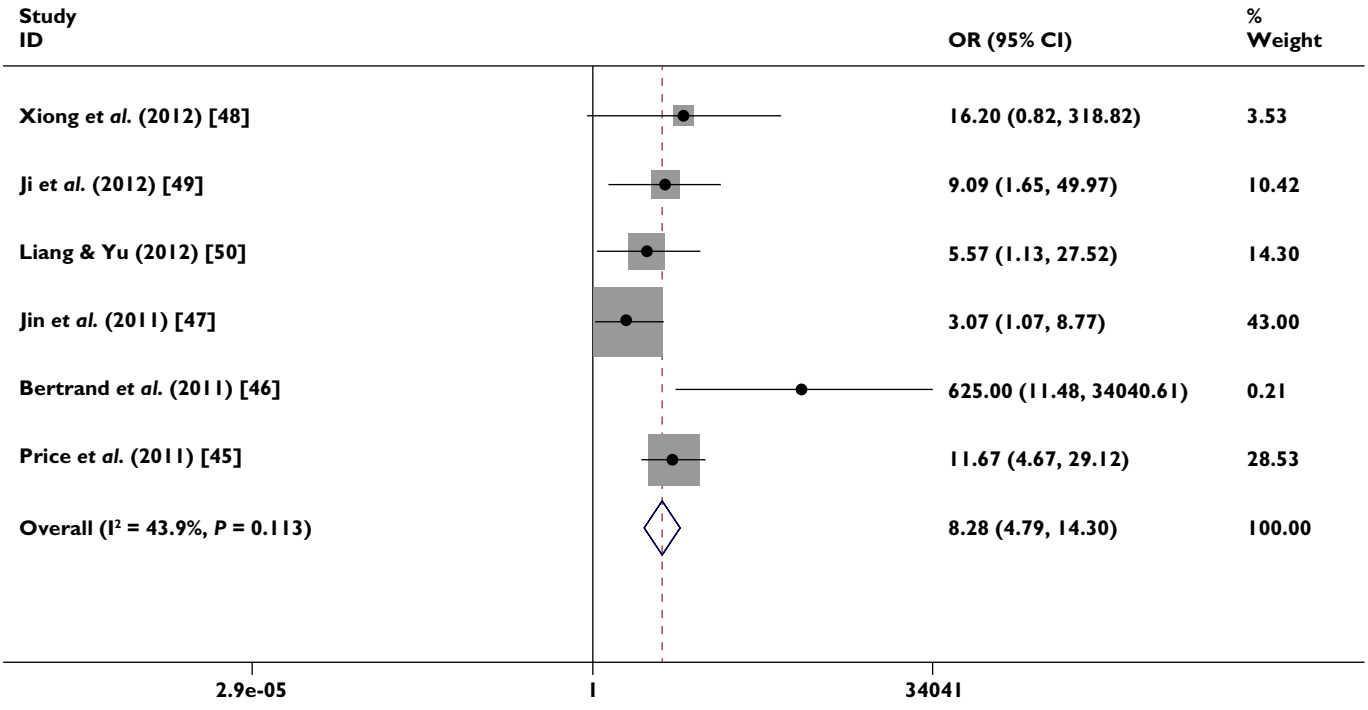

Figure 10

Forest plot of the effectiveness of propranolol compared with steroids in treating IHs in RCT subgroup analysis by good degree

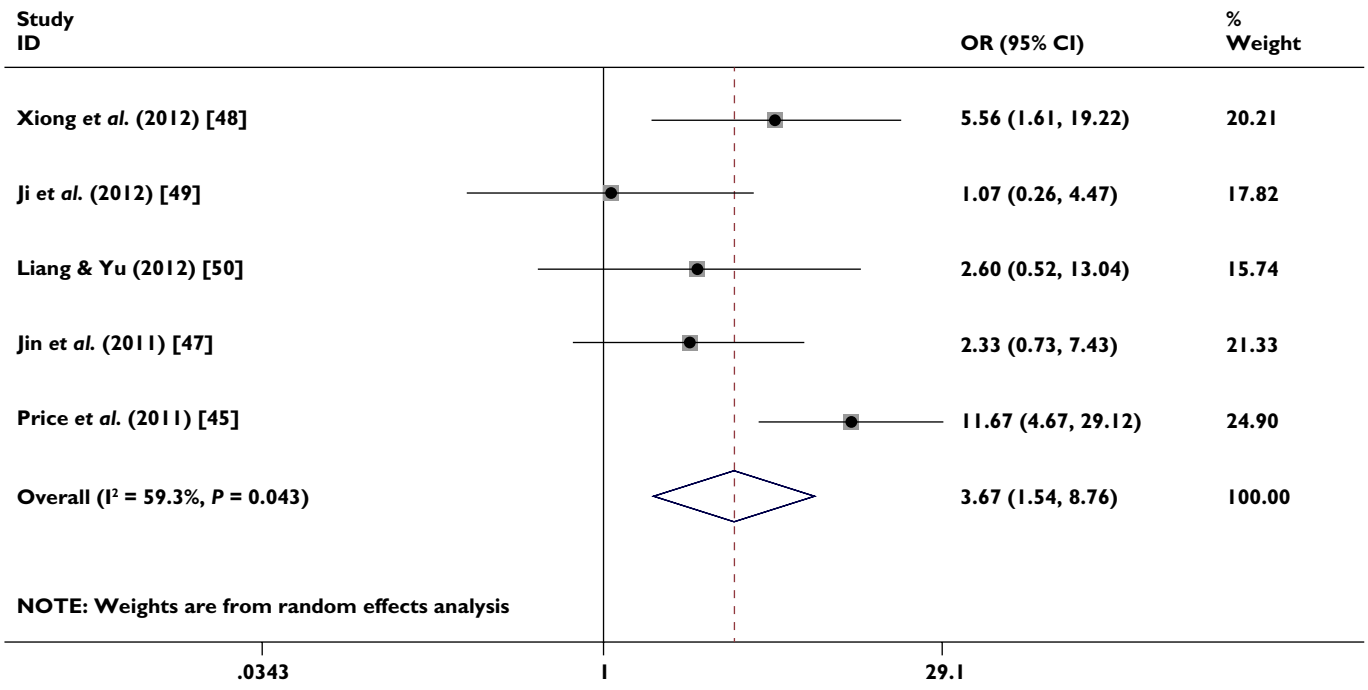

Figure 11

Forest plot of the effectiveness of propranolol compared with steroids in treating IHs in RCT subgroup analysis by excellent degree

which were limited with a smaller sample size. Secondly, given that only one study examined the effectiveness of propranolol *vs.* interferon-α, we were unable to conduct further subgroup analysis.

Despite of above limitations, the current study provided strong evidence for propranolol as a first line therapy for IHs. Studies analyzing the side effects and clinical follow-up of propranolol in treating IHs were lacking. Additional papers including case-control design studies with larger sample sizes should be launched to check and extend the conclusion.

Competing Interests

All authors have completed the Unified Competing Interest form and declared: no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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